IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: SELA=5

In re Application of:	)	Confirmation No.: 3015
	)	
Yoram SELA	)	Examiner: Jake Minh Vu
	)	
Appln. No.: 10/500,634	)	Group Art Unit: 1618
	)	
Filed: January 24, 2005	)	Washington, D.C.
	)	
For: EXTENDED RELEASE COMPOSITIONS COMPRISING AS ACTIVE COMPOUND VENLAFAXINE HYDROCHLORIDE	)	

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window
Randolph Building, Mail Stop
401 Dulany Street
Alexandria, VA 22314

Sir:

I, the undersigned Yoram SELA, Ph.D., hereby declare and state as follows:

I am the inventor of the above-identified application. My curriculum vitae is attached hereto.

I understand that the examiner examining my above-identified application has cited EP0919236 of Heiligenstein and considers that it would be obvious to substitute venlafaxine hydrochloride for duloxetine in the enteric formulation disclosed by Heiligenstein. It is further my

understanding that the examiner considers that the product of such substitution would fall within the scope of the claims of my patent application.

In order to test the examiner's thesis, my laboratory has attempted to reproduce the enteric formulation of Heiligenstein, substituting venlafaxine hydrochloride for duloxetine and to determine the dissolution characteristics of the obtained product. Due to technical considerations resulting from the differences between the duloxetine and venlafaxine physicochemical characterizations, some modifications had to be done, each of which will be mentioned below. However, in my opinion, none of the changes would be expected to substantially change the dissolution characteristics of the product of the process.

The following experiment was conducted in my laboratory by me or under my direct supervision and I can testify that the materials and protocols specified below and the results shown below are all true and correct to the best of my knowledge and belief.

Manufacture of Heiligenstein Formulation Substituting Venlafaxine HCL

Raw materials:

Venlafaxine HCL, supplied by KRKA.

Excipients: as listed in the Heiligenstein sample.

Equipment: Uniglatt 6", equipped with Wurster column.

4" fluid bed, equipped with Wurster column.

Batch sizes 150-300gr.

Stage 1 - Drug Layering

We could not make it exactly as the original Heiligenstein procedure: the exceptionally high concentration of HPMC/highly concentrated coating solution and its sticky characteristics caused us to change to new suspension: talc(10%)/HPMC(5cp) 4.5%/venlafaxine 85%. The suspension concentration was 7.5%, FBD 4" was used.

Lot-VF100712/A

Stage 2 - Subcoating

Subcoating suspension was prepared according to the Heiligenstein patent; the suspension concentration was 11%, containing talc 29%/sucrose 14%/HPMC 57%.

VF100712/B

Stage 3 - The Delayed Release Layer

The coating suspension was prepared according to the patent; its concentration was 7%. The suspension contained talc(20%)/TEC(13%)/HPMCAS 3cp (67%).

Two coating layers were prepared:

VF100712/C1 - 40% w/w

VF100712/C2 - 60% w/w

Stage 4 - The "Finishing" Layer-Cosmetic Coating

The suspension was prepared according to the Heiligenstein patent. The suspension: HPMC(64%)/talc(5%)/titanium dioxide(21%)/PEG 400(10%) (which was added instead of PG as plasticizer).
The finishing suspension was added on lot VF100712/C2 (60% coating) and is designated **VF100712/D.**

In each stage, samples were taken to analysis-assay and dissolution. The results are as shown in Figure 1. The first three lines of the graph, which appear in the upper part of the graph, show the two formulations with different amounts of delayed release layer but without a finishing layer (VF100712/C1 and VF100712/C2, and the formulation with a finishing layer (VF100712/D). When dissolved in IFS, which is an intestinal buffer, pH 6.8, it can be seen that all three of these compositions completely released the active ingredient in less than 1 hour, as would be expected for an enteric formulation. The bottom three lines of Figure 1 show the same formulations dissolved in GFS, which is a gastric buffer at pH 1.2. Again, as expected for an enteric formulation, the total

active ingredient released by each over 24 hours was extremely small.

Thus, the venlafaxine•HCL beads prepared according to the Heiligenstein process (11.2 mg, for comparison purposes) shows typical enteric characteristics - less than 10% in 2 hours, and about 10% in 24 hours in GFS and prompt release in less than 30 minutes in IFS.

For the purpose of comparison, I have retrieved experimental results of experiments conducted prior to the filing of the present application. Product "A" is a product within the scope of the claims of my above-identified application. This product was made by a process very similar of that of Example 5 of my above-identified application in accordance with the following:

Product "A"

1. Layering:

150gr NP's

150gr venlafaxine

4.5gr PVP K90

112.5gr water + 665gr ethanol as solvent

2.First coating:

150gr coated NP's from stage 1

3.75gr PVP K30, dissolved in 60gr ethanol

3.Second layer - the ER layer:

Ethocel 45 cp 20gr

DBS 2 gr

330gr ethanol as solvent.

Product "A" was tested for dissolution characteristics at GFS and the IFS pH's. The results of the dissolution test are shown in Figure 2 attached hereto. It can be seen that on testing using USP I at 50 RPM, the results are substantially identical whether using pH 1.2 or pH 6.8. Similarly, the results are substantially identical when increasing the RPM to 100 or when using USP II at pH 6.8 at 75 RPM. This establishes that the dissolution characteristics are pH-independent and provide controlled extended release that is continuous over a 24 hour period.

Other experiments conducted prior to the filing of the present application show the release characteristics of the same product of the above-identified application compared with those of the product identified in my above-identified patent application as the Brand product, which is the venlafaxine hydrochloride extended release product approved by the FDA and sold under the name EFFEXOR XR. In this test, IFS was chosen as the representative method (IFS/50RPM/90cc, no

enzymes). The compound of the present invention tested is the same product "A" referred to above. It can be seen from Figure 3 that the dissolution characteristics of the product of the present invention are substantially identical, and certainly bioequivalent, to the dissolution characteristics for EFFEXOR XR.

The experimentation reported above, originally conducted prior to the filing date of the present application, was all conducted in my laboratory, either by me or under my direct supervision, and therefore I can attest with first-hand knowledge as to the accuracy of the experimental parameters and results reported herein.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

16.8.2010 /Yoram Sela/

Date Yoram SELA, Ph.D.

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FIGURE 1

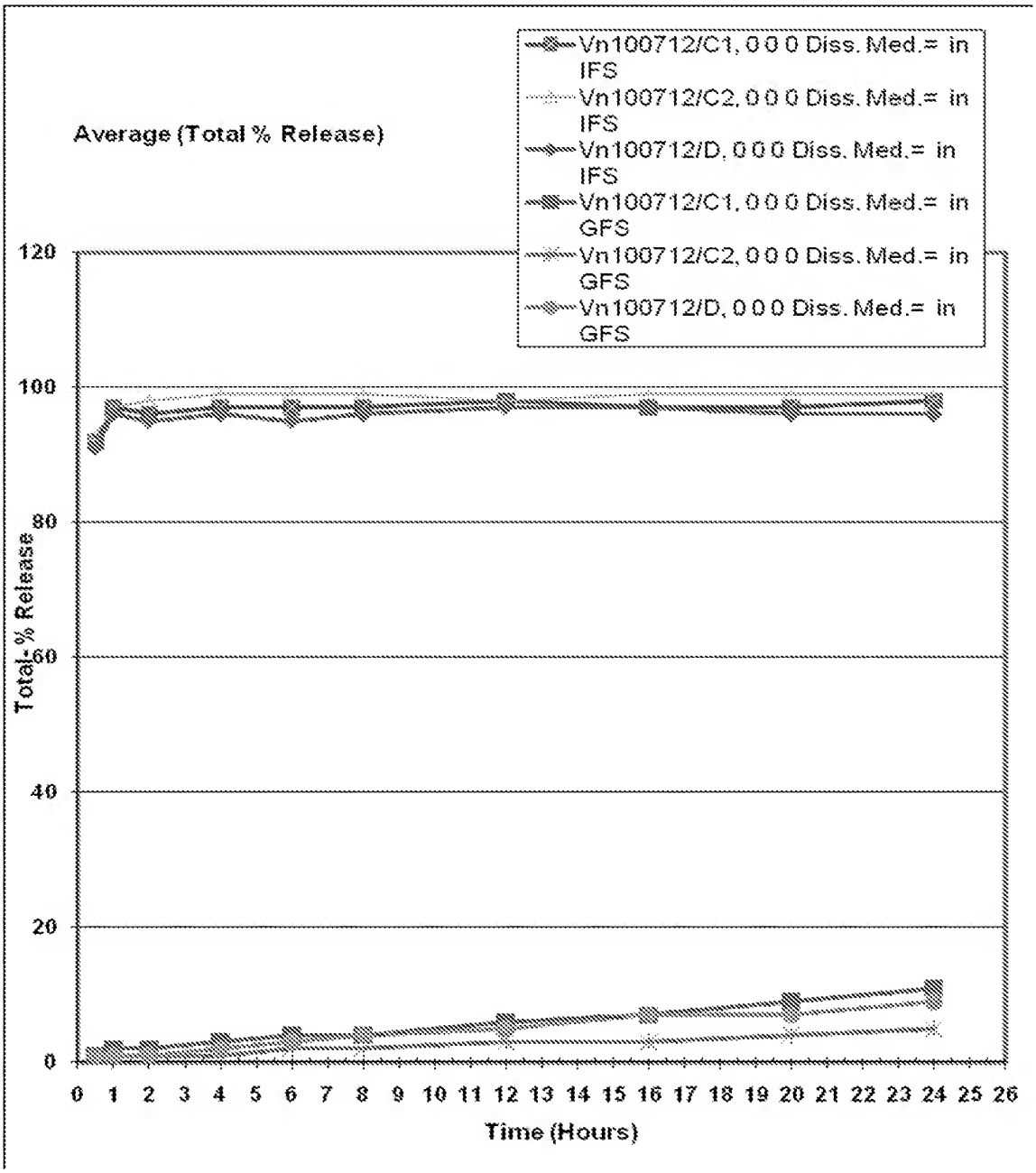

Average (Total % Release)
Vn100712/C1, 0 0 0 Diss. Med.= in IFS
Vn100712/C2, 0 0 0 Diss. Med.= in IFS
Vn100712/D, 0 0 0 Diss. Med.= in IFS
Vn100712/C1, 0 0 0 Diss. Med.= in GFS
Vn100712/C2, 0 0 0 Diss. Med.= in GFS
Vn100712/D, 0 0 0 Diss. Med.= in GFS
Total- % Release
120
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Time (Hours)

FIGURE 2

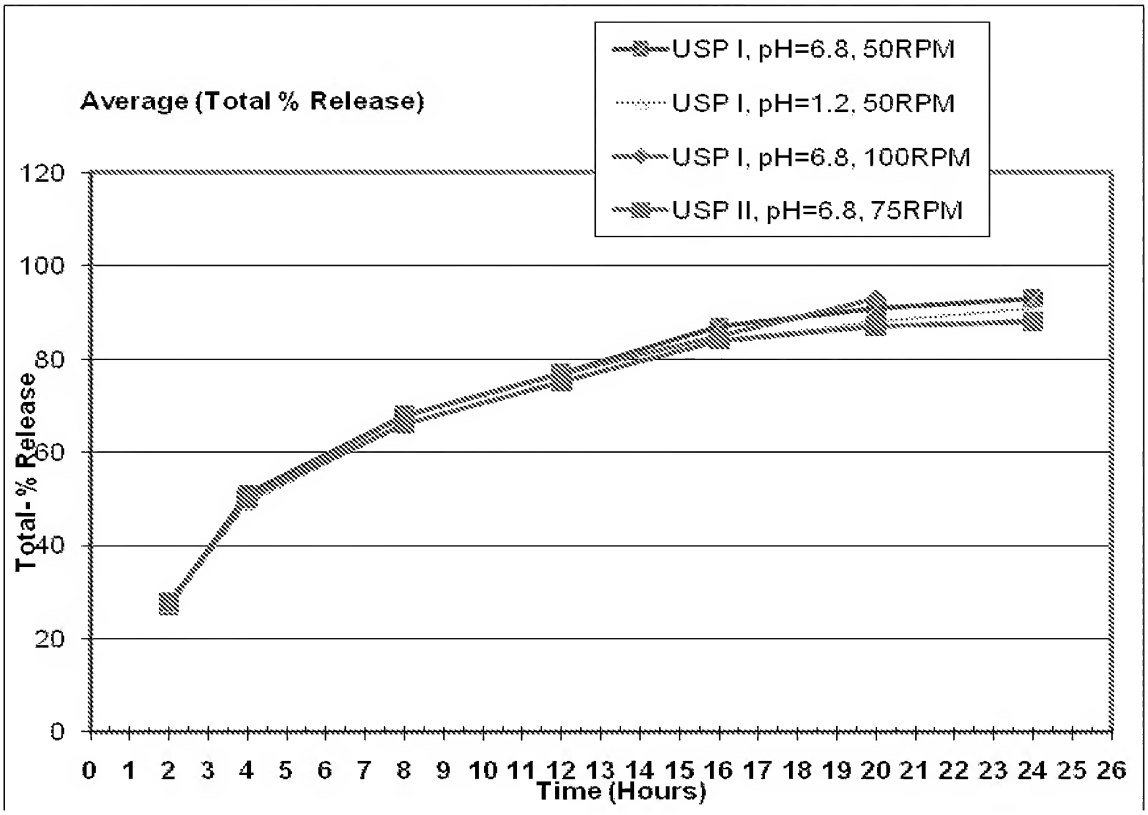
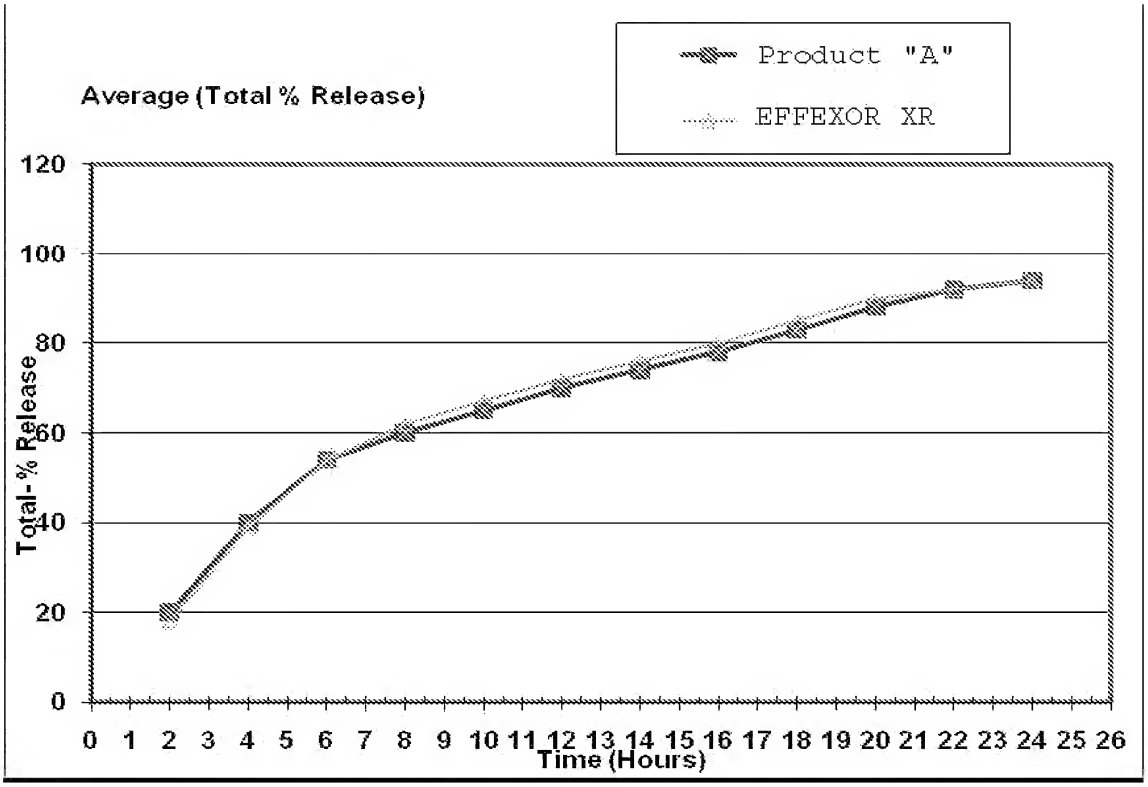

Average (Total % Release)
USP I, pH=6.8, 50RPM
USP I, pH=1.2, 50RPM
USP I, pH=6.8, 100RPM
USP II, pH=6.8, 75RPM
Total- % Release
0
20
40
60
80
100
120
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Time (Hours)

FIGURE 3


Product "A"
EFFEXOR XR
Average (Total % Release)
Total - % Release
120
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Time (Hours)

June -2009

YORAM SELA- CURRICULUM VITAE

Academic Background

1982 - 1985	B.Sc. in Agriculture, Hebrew University of Jerusalem.
1985 - 1987	M.Sc. Casali Institute of Applied Chemistry, Hebrew University of Jerusalem.
1987 - 1991	Ph.D., Casali Institute of Applied Chemistry, Hebrew University of Jerusalem.

Occupational and Research Experience

1991 - 2000	Teva Pharmaceuticals, Pharmaceutical R&D-,"Drug Delivery" Section Manager
2000 - 2004	Karma Pharm Ltd., Co-Founder and Director, R&D
2004 - 2008	Lycored Ltd., V.P. R&D
2008-	Nesher Solutions, VP R&D

Other Activities

2001 - 2003	President, The Israeli Controlled Release Society.
2003-2008	Co-Founder and director, E-Pill Ltd.
2004-	Entrepreneur - Calcident, Incubator Company
2008-	Co-Founder and director, Pharma2B Ltd.